PATENT
Attorney Docket No: 27373/34978A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Linquist *et al.*

Filed: June 9, 2000

For: "Recombinant Prion-Like Genes and Proteins and Materials and Methods Comprising Same"

Group Art Unit: 1646

Examiner: M. Brannock

Application No. 09/591,632

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on October 22, 2003.

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF

SUSAN LINDQUIST, Ph.D.

I, Dr. Susan Lindquist, declare and state as follows:

I. Introduction

1.1 I am a co-inventor of the subject matter of the above-identified patent application (hereinafter "the patent application"). I am experienced in the arts of molecular biology and, more specifically, am an active researcher in the biology of prions and prion-like proteins. To illustrate the breadth of my experience, a copy of my *curriculum vitae* is attached hereto as Appendix A. I am currently the Director, Whitehead Institute for Biomedical Research and Professor of Biology at Massachusetts Institute of Technology.

1.2 I have read the referenced patent application and the Office Action dated April 22, 2003 (hereinafter "the Office Action") in connection with the referenced patent application. I submit this declaration to address issues raised by the U.S. Patent and Trademark Office (USPTO) in the Office Action and to provide evidence to the USPTO that may be relevant to the patentability of the pending claims. I hereby affirm that, to the best of my knowledge and belief, factual

statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

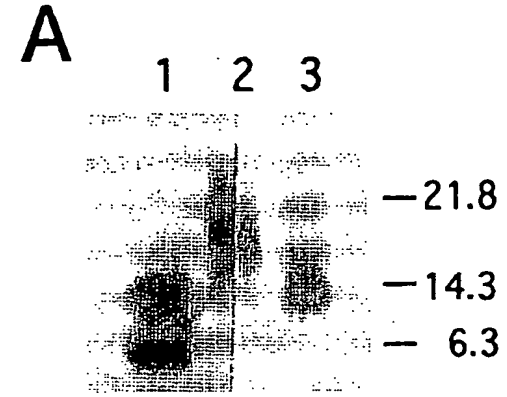
II. The Gregori et al. document

2.1. In the Office Action, many of the rejections were based, in whole or in part, on the alleged teachings in Gregori *et al., J. Biol. Chem., 272*: 58-62 (1997), referred to herein as "Gregori." I have reviewed the analysis in the Office Action and also reviewed Gregori and disagree with the Patent Office's characterization of Gregori:

> Gregori et al disclose a polypeptide comprising a self-aggregation domain of Amyloid-β protein (residues 1-40) comprising the substitution of residue 40 with a cysteine residue having a reactable side chain and further modified with a metal ion (gold), see col 1 of page 59. Gregori et al further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60, therefore one of ordinary skill in the art would expect that the gold labeled side chain is exposed to the environment in an ordered aggregate because the gold does not appear to inhibit aggregation as would be expected if the gold was buried in the interior of the aggregate.
>
> (Office action at pp. 2-3.)

As I explain below Gregori fails to disclose that the labeled peptide forms ordered aggregates, and in fact, has data suggesting that it does not.

2.2 The Patent Office's analysis of Gregori is based in part on a misinterpretation of Figure 2A, reproduced below:



2.3 According to Gregori, lane 1 of Figure 2A depicts an electrophoretic migration pattern of an unlabeled, cysteine-substituted amyloid beta (Aβ) protein ($A\beta_{1\text{-}39C40}$, which is amyloid beta 1-40 wherein the natural 40th residue is substituted with cysteine) in a polyacrylamide gel. (See Figure 2 legend in Gregori) Protein bands were detected via Western blotting using 6E10 antibodies that recognize Aβ. This lane shows that monomer and dimer bands of Aβ appear to migrate at roughly the same distances as the 6.3 kDa and 14 kDa molecular weight markers along the right side of Figure 2A. Gregori states that "because gel electrophoresis analysis was performed under denaturing, but not reducing, conditions . . . the control lane with the peptide alone shows the monomer and the dimer forms of $A\beta_{1\text{-}39C40}$."[1] (Figure 2 legend.) A second control lane, lane 3, shows the migration pattern of unconjugated (i.e., "free") Nanogold. The free Nanogold was detected by silver staining and appears to have migrated as a smear at roughly the same location as the 14.3 kDa marker. Lane 2 of the same gel shows the migration pattern of a Nanogold-labeled $A\beta_{1\text{-}39C40}$ protein ("$A\beta^{Au}$"). This lane shows a smear roughly spanning the distance between the 14.3 and 21.8 kDa molecular weight markers. Regarding this smear on the gel, Gregori states that lane 2 shows that the $A\beta^{Au}$ "..migrates as a complex of 17 kDa." (See figure legend for Figure 2, page 60).

[1] A person of ordinary skill would interpret this dimer as representing a disulfide-linked pair of Aβ molecules, linked at the cysteines, rather than aggregated Aβ.

2.4 The migratory patterns in control lanes 1 and 3 permit only one reasonable interpretation of lane 2. Specifically, one of ordinary skill in the art would conclude that lane 2 of Figure 2A simply shows an $A\beta_{1\text{-}39C40}$ *monomer* conjugated to a single Nanogold particle. In other words, the approximately 6.3 kDa peptide monomer, when complexed with the approximately 14.3 kDa Nanogold, forms a gold-labeled peptide that migrates as a smear of about 17-21 kDa. (Simple addition of ~6 kb $A\beta_{1\text{-}39C40}$ monomer + ~14 kDa Nanogold would place the conjugated protein within the smear of lane 2). Although the authors describe this as an $A\beta^{Au}$ "complex," the only reasonable interpretation of this statement, in the context of the data presented, is that it is a complex of one peptide subunit with one Nanogold particle. A person of ordinary skill would not interpret this portion of Gregori as teaching that $A\beta^{Au}$ is forming aggregates with itself, [2] let alone higher ordered aggregates contemplated in the patent application.[3] There is no evidence in Gregori that $A\beta^{Au}$ forms dimers, let alone higher ordered aggregates.

2.5 The Patent Office characterized Figure 2A as follows

> This figure shows that the gold labeled peptide migrates under these conditions as a complex with a higher molecular weight than the unlabeled monomer and dimer shown in lane 1. This is explicitly taught in the figure legend at line 13.
>
> (Office action at p. 3.)

As explained in the preceding paragraph, the higher molecular weight of the $A\beta^{Au}$ "complex" is attributable to the effect of one Nanogold moiety on the total molecular weight -- not to the formation of protein aggregates. The "complex" is one amyloid beta peptide with one Nanogold moiety -- not a higher-order aggregate of labeled peptides.

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[2] One of ordinary skill would have expected from the data that (a single) Nanogold conjugated to an Aβ *dimer* would migrate at roughly 28 kDa, well above the smear of lane 2.

[3] As defined in the specification, "...the term SCHAG is an acronym for Self-Coalesces into Higher-ordered AGgregates. By "higher ordered" is meant an aggregate of at least 25 polypeptide subunits, and is meant to exclude the many proteins that are known to comprise polypeptide dimers, tetramers, or other small numbers of polypeptide subunits in an active complex." (See specification at page 6, lines 13-17)

2.6 Referring again to the Office action, the Patent Office concluded, "Gregori et al further disclose that the labeled peptide forms ordered aggregates see col 1 of page 60." Column 1 of page 60 includes an analysis of the data in Figure 2A, and as I explain above, that data does not support a conclusion that ordered aggregates of the gold-labeled Aβ are forming.

2.7 The first full paragraph of column 1 of page 60 also provides an analysis of the ability and behavior of Aβ in forming complexes with a proteasome. Referring to this paragraph, the Patent Office says, "One of ordinary skill in the art appreciates that Col 1 of page 60 discusses the difficulties encountered during the study of the amyloid/proteosome interaction *because* of the inherent property of the gold labeled amyloid protein to self aggregate . . . ." (See Office action at pp. 3-4.) In actuality, this paragraph of Gregori et al. relates to an experiment using ordinary "Aβ", not an experiment using "$A\beta^{Au}$", which is the term Gregori uses to describe the cysteine-substituted, gold-labeled $A\beta_{1\text{-}39C40}$ molecule. (Subsequent paragraphs of the article dicuss the proteasome-$A\beta^{Au}$ complex and use the term "$A\beta^{Au}$" when describing it.) There is nothing in Gregori et al. that discloses or suggests that the cysteine-substituted, gold-labeled amyloid beta peptide forms aggregates with itself, let alone higher ordered aggregates of the type discussed in the patent application.

2.8 The Patent Office also "noted that Applicant does not assert that the aggregates would not be expected to form nor that the reactive cysteine would not be expected to be exposed." (Office action at p. 4.) As explained above, the *data and analysis* provided by Gregori et al. gives no suggestion whatsoever that the cysteine-substituted, gold-labeled amyloid beta forms aggregates or is expected to form aggregates.

2.9 Moreover, it is my opinion that the Nanogold-labeled Aβ peptides would not be expected to form higher ordered aggregates of the type that an unsubstituted, unlabeled Aβ peptide might form with itself. As shown in Figure 2A, the size of the Nanogold moiety is substantial compared to the size of the amyloid beta peptide moiety, representing perhaps 70% or more of the total size (using the molecular weight size markers and migration patterns of free Nanogold and Aβ as the criteria.) Gregori also teaches that the 1.4 nm Nanogold particle caused "anomalous behavior of Aβ in solution." (Page 60, column 1.) Based on my experience with Nanogold and with aggregating proteins such as prions, I would not predict, and do

not believe that a person of ordinary skill in the art would predict, that Gregori's cysteine-substituted, Nanogold-labeled Aβ would self-aggregate into higher ordered aggregates as contemplated in the patent application. Instead, the Nanogold would be expected to cause steric hinderance to inhibit aggregation

2.10 Several claims of the patent application recite "polymer", "fibrous polymer", or filamentous polymer" limitation(s). (See, e.g., claims 67, 120, 134-141, and 143) There is absolutely no mention in Gregori et al of Aβ or $A\beta^{Au}$ forming fibers or polymers, either via self aggregation or via proteasome interactions. In fact, Figure 4A-D demonstrate that a single $A\beta^{Au}$ peptide cross-linked to a single proteasome. (See also page 60, right column of Gregori et al.) Further, Figure 4A-D demonstrate that the $A\beta^{Au}$-proteasome complex is still visible as a barrel-shaped structure, not as a polymer or fiber.

2.11 For the reasons outlined above, it is my opinion that the Patent Office has mischaracterized the teachings of Gregori et al. As a consequence, the Patent Office has also misapplied Gregori et al. as a prior art reference alone (paragraph 2 of the Office action, anticipation) or in combination with other documents (paragraph 5, obviousness when combined with a King publication).

III. The Stayton document combined with the Prusiner patent.

3.1 In the Office action three of the Patent Office's rejections are based, at least in part, on the alleged motivation to combine the teachings of Prusiner et al., U.S. Patent No. 5,750,361 (Prusiner) with an article by Stayton *et al.,J. Biol. Chem., 263*: 13544-48 (1988) (Stayton). The Patent Office alleges that a person of ordinary skill in the art would have been motivated to combine the teachings of these documents (sometimes with additional documents) and would have arrived at certain embodiments of the invention claimed in the patent application. In this section I explain that these allegations are scientifically flawed.

3.2. With respect to Stayton, the Examiner states:

> For example, Stayton et al. disclose a method of labeling a polypeptide comprising identifying residues having side chains exposed to the environment...and substituting these residues with residues having a reactable side-chain and further modifying the reactive side chains with a fluorescent agent (see the abstract

> and col 2 of page 13544). (See page 9 of the Office Action)

The Examiner asserts that one of ordinary skill in the art would be able to apply the teachings of Stayton to polypeptides comprising prion aggregation domains:

> Therefore, it would have been obvious to one of ordinary skill in the art, with reasonable expectation of success, to produce a polypeptide comprising a prion aggregation domain for use in an assay to detect prion aggregates (and thus producing the aggregates themselves) labeled with a fluorescent or other spectrophotometrically-detectable substituent...and to accomplish this by selecting a residue having a side chain exposed to the environment and replacing that residue with one having a reactable side chain and then further modifying the side chain with a fluorescent dye, as taught by Stayton et al. and/or a biotin molecule as is old in the art. The motivation to do so was provided by U.S. Patent No: 5750361 wherein it is stated that the polypeptide should be modified as described in the art and that amino acids could be substituted as long as the change does not effect complex formation...(See Office Action at page 10)

I find both technical and logical flaws in the Patent Office's analysis.

A. The techniques of Stayton are not transferable to prions.

3.3 The Stayton reference describes the "crystallographic" selection of two residues in a cytochrome protein for mutagenesis to assist with analysis of heterologous protein-protein associations (cytochrome-myoglobin interactions). Stayton's technique for selecting residues to modify would not be expected to work with SCHAG proteins such as those described in the patent application.

3.4 More specifically, a person of ordinary skill in the art who worked in this field in 1999-2000 would have expected that Stayton's crystallographic analysis of cytochrome protein would be ineffective and technically unfeasible with SCHAG proteins. Aggregating, fiber-forming proteins were understood in the art at this time to be extremely difficult, or impossible, to crystallize. Thus, while Stayton was able to use X-ray diffraction to localize amino acids in a cytochrome protein for modification, a person skilled in the art would not expect such techniques to be

feasible with SCHAG proteins. In fact, to my knowledge no SCHAG proteins have been crystallized in the same structure as in the fiber form, despite many years of effort by scientists working in the field.

3.5. Even if one were able to crystallize SCHAG proteins, a person of ordinary skill would not expect the crystals to yield structural data that is useful for predicting the positions of amino acids within the protein when the protein forms higher ordered aggregates such as prion fibers. As described in the patent application (See, e.g., page 6, lines 22-25; page 1, lines 22-25; and page 3, lines 23-25), SCHAG sequences exist in multiple conformational states. Hence, a stable soluble state of a prion and a stable, fiber-forming state are observed and described in the literature. A person familiar with this field of research would not expect that structural data gleaned from a theoretical crystalline state would reflect the structure (i.e., the spatial orientation of amino acids) in an alternative state. In other words, even if the difficulties in forming crystals were overcome so that Stayton's methodology could be practiced on a SCHAG protein, a person of ordinary skill still would not be motivated to perform this analysis because the resultant data would not be expected to be relevant for the identification of specific residue locations (in the fiber-forming state) suitable for mutation. In fact, it is commonly believed that proteins undergo a considerable change in structure when converting to the fiber form, as occurs with the PrP protein described below. Thus, it would not be possible to follow the teachings in Stayton to identify potential amino acids for substation with amino acids with reactable side chains.

B. No motivation to combine teachings.

3.6 In the Office action the Patent Office acknowledges that Prusiner does not teach the subject matter of the invention when the Patent Office states, "U.S. Patent No. 5,750,361 does not specifically recite that the act of labeling the polypeptide include the steps of choosing an amino acid residue in the sequence having a side chain that is exposed to the environment and substituting this amino acid with one having a reactive side chain." (Office action at p. 9.) However, the Patent Office nonetheless says that there is no invention because "these steps are old

and well established in the art of protein complex detection." (Id.) The Patent Office cites Stayton as an example of this allegedly well established technique.

3.7 In my opinion, a person of ordinary skill in the art would not agree with the Patent Office's analysis. In fact, a person of ordinary skill would find the Patent Office's analysis illogical, and would have been dissuaded from following it.

3.8 First, a person of ordinary skill would be evaluating Prusiner for the purposes set forth in Prusiner, not for the purposes set forth in the instant patent application, which had not yet become publicly available. In stark contrast to the instant application where labels that do not interfere with complex formation are preferred, Prusiner was concerned with detection of prion protein complexes in the context of screening for compounds which inhibit prion complex formation. In this context, a person of ordinary skill is interested in techniques which are (1) rapid and inexpensive, to permit cost-effective screening of thousands or even millions of compounds; and (2) reasonably predictive of prion protein behavior *in vivo*, where prion aggregation is pathogenic. Prusiner's techniques serve as the logical benchmark for judging whether there is motivation to try a different technique: techniques which are slower, more expensive, and offer potentially less predictive value are illogical, and there is no motivation to try them.

3.9 Prusiner teaches a complex-inhibition assay that can be practiced with *unaltered* PrP protein sequences, in which PrP is permitted to form a complex which is detectable by simple sedimentation and protease resistance assays. (Column 11). Prusiner further teaches a displacement assay which uses labeled PrP, such as PrP labeled with radioisotopes, fluorescent dyes and spectrophotometrically-detectable chromophores. (Paragraph bridging columns 11-12.) Neither of these techniques require alteration of the primary amino acid sequence, so they are already faster and less expensive than what the Patent Office has suggested (by combining Prusiner and Stayton). In contrast, combining Prusiner and Stayton is a slow and expensive process involving crystallization of a protein that is difficult, if not impossible, to crystallize and complex analyses of the spatial position of atoms to determine an amino acid suitable for alteration.

3.10 Even if the techniques of Stayton could be combined with Prusiner, a person of ordinary skill would be reluctant to do so, because the alteration of the PrP amino acid sequence would risk making the assay less predictive of PrP complex formation *in vivo*. Because any non-natural amino acid alteration makes the assay system less similar to an *in vivo* system containing the wild-type protein, a person of ordinary skill would not choose to alter the primary sequence (as taught by Stayton) in the absence of a benefit to doing so.

3.11 The Patent Office dismissed the analysis in the preceding paragraph, stating that "One of ordinary skill in the art appreciates that most of the techniques of labeling recited by the Prusiner patent (e.g. at col 11 bridging 12) involve the use of chemical substituents to the native protein- thus changing the chemical properties of the native amino acid that the substituent is attached to." (Office action at pp. 11-12.) While this may be true, it is also true that not all changes are created equal. Attachment of a radioisotope generally has virtually no effect on primary, secondary, or tertiary structure of a protein. A person of ordinary skill appreciates that alteration of the primary sequence is more likely to alter all of these properties than attachment of a radioisotope, fluorophore, or chromophore to a native sequence. There are potential disadvantages that would have been appreciated by a person of ordinary skill, but no clear advantages, to doing what the Patent Office proposed.

3.12 The Patent Office also cited Prusiner column 7, lines 30-36, as providing a "desirability" of making PrP variants. A person of ordinary skill in the art would read the entire cited paragraph of Prusiner to provide proper context. The only variant that Prusiner taught might be "desirable" was a variant corresponding to a known pathogenic mutation which causes two forms of disease. (See column 7, lines 35-41.) A person of ordinary skill in the art understands the desirability of using a pathogenic form of a gene/protein to screen for therapeutics to treat the pathology. However, Prusiner does not teach a "desirability" of making other PrP variants for other purposes.

3.13 To summarize, the Patent Office failed to identify any benefit to modifying Prusiner's PrP proteins using techniques taught by Stayton, and in fact, as I explained in the previous paragraph, the cost and risk of doing so appears to outweigh any benefit. A person of ordinary skill in the art simply has no motivation

to alter Prusiner in the manner suggested by the Patent Office. I categorically disagree with the Patent Office's assessment that "in following the methods taught in Prusiner, the artisan would be motivated to make the claimed product."

3.14 The Patent Office's succinct logic was that "Substituting amino acids with amino acids having reactable side chains for the purpose of attaching labels to the protein to monitor protein interactions is old and well established in the art, e.g. Stayton et al. is cited as evidence that such techniques were well known in the art." (See Office Action at pages 10-11) However, as I explained in the preceding paragraphs, just because a technique is known in the art does not mean that there is any motivation or logic in applying the technique to a particular circumstance or problem. The instant patent application modifies proteins to create new properties that the protein will have only in the assembled state. The literature cited by the Patent Office did not provide this motivation. In fact, as explained above, the literature cited by the Patent Office is directed to purposes where scientists do not want to alter the properties of the prion proteins.

IV. Certification

4.1. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Susan Lindquist

Date: 10/21/03

Susan Lee Lindquist

Curriculum Vitae

ADDRESS

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EDUCATION

1976 Ph. D. in Biology, November
Harvard University, Cambridge, Massachusetts
Thesis Advisor: Matthew Meselson

1971 B. A. in Microbiology with High Honors
University of Illinois, Champaign-Urbana, Illinois
Research Advisor: Jan Drake

EMPLOYMENT

2001–present Director, Whitehead Institute for Biomedical Research
Professor of Biology, Massachusetts Institute of Technology
Cambridge, Massachusetts

1988–2001 Investigator
Howard Hughes Medical Institute
The University of Chicago, Chicago, Illinois

1988–2001 Professor, Department of Molecular Genetics & Cell Biology
The Committee on Genetics
The Committee on Developmental Biology
Cancer Research Center
The University of Chicago, Chicago, Illinois

1984–1988 Associate Professor
The University of Chicago, Chicago, Illinois

1978–1984 Assistant Professor, Department of Biology
The University of Chicago, Chicago, Illinois

1976–1978 Postdoctoral Training
The University of Chicago, Chicago, Illinois
Advisor: Hewson Swift
Fellowship Support: The American Cancer Society

REPRESENTATIVE HONORS AND AWARDS

Member, American Philosophical Society, 2003.
Dickson Prize in Medicine, University of Pittsburgh, 2002-2003.
Named one of the 50 most important women in science, Discover Magazine, 2002.
Honorary Doctor of Science, Ursinus College, Collegeville, Pennsylvania, 2002.
Honorary Doctor of Science, Pine Manor College, Chestnut Hill, Massachusetts, 2002.
Burroughs Wellcome Foundation Visiting Professorship, University of Arizona, 2001.
Novartis Drew Award in Biomedical Research, 2000.
Albert D. Lasker Professor of Medical Sciences, The University of Chicago, 1999-2001.
Member, National Academy of Sciences, 1997.
Fellow, American Academy of Microbiology, 1997.
Member, American Academy of Arts and Sciences, 1996.
MERIT Award, NIH, NIHMS (GM25874), 1978-Present.

RECENT HONORARY LECTURES

Swift Lecture, University of Chicago, 2003.
Dickson Prize Lecture, University of Pittsburgh, 2003.
Harvey Lecture, Rockefeller University, NY, 2003.
Keynote Address, Gordon Conference on Triplet Repeat Disorders, Lucca, Italy, 2003.
Keynote Address, University of Pennsylvania Cancer Center, 2003.
The Gladstone Institute Distinguished Visiting Scholar Lectures, San Francisco, CA, 2003.
Fae Golden Kass Lecture, Harvard Medical School, 2003.
Roger Herriott Lecture, Johns Hopkins Bloomberg School of Public Health, 2003.
Evans Medicine/Research Seminar Series, Boston University Medical Center, 2003.
Efraim Racker Lectureship in Biology and Medicine, Cornell University, 2002.
Allan C. Wilson Memorial Lectures, University of California at Berkeley, 2002.
Don W. Fawcett Lectures, Harvard Medical School, 2002.
Arthur M. Sackler Lecture, National Academy of Sciences, 2002.
Institute for Systems Biology Inaugural Symposium, Seattle, WA, 2002.
Carnegie Institution Capital Science Lecture, Washington, D.C., 2002.
Cambridge University (UK)-MIT Institute Distinguished Lecture Series, 2002.
McKusick-Nathans Institute of Genetic Medicine Inaugural Symposium, 2001.
Keith Porter Lecture, ASCB Annual Meeting, 2001.
Katharine Dexter McCormick Lecture, Stanford University, 2001.
C.B. Van Neil Lecture, Hopkins Marine Station, Stanford University, 2001.
Searle Forum Lecture, Northwestern University, 2001.
Burroughs Wellcome Fund Lectures, University of Arizona, 2001.
Francis Schmitt Lecture/Department of Biology, Massachusetts Institute of Technology, 2001.
Juanita Greer White Distinguished Lecture, University of Nevada, 2001.
University Lecture Series, The University of Texas Southwestern Medical Center, 2001.
BASF Lecture, Brandeis University, 2001.
Keynote Address, EuroConference & EMBO Workshop, Molecular Chaperones, Spain, 2001.
Biosciences Distinguished Lecturer, Lawrence Berkeley National Laboratory, 2000.
Women Leaders in Science Seminar, University of California-San Francisco, 2000.
Kenneth Sparks-Julia Fisher Memorial Lecture, University of Connecticut, 2000.
Robert & Esther Stadtler Lecture, University of Texas MD Anderson Cancer Center, 2000.

Research School of Biosciences Annual Lecture, University of Kent, England, 2000.
John S. Colter Lecture in Biochemistry, University of Alberta, Canada, 2000.
Novartis-Drew Award Lecture, Drew University, 2000.
Fritz-Lippman-Lecture, German Society of Biochemistry and Molecular Biology, Munich, 2000.
Dean's Lecture, Mount Sinai School of Medicine, 2000.
University Lecture, The Rockefeller University, 2000.
TSRI Graduate Program Distinguished Lecture, The Scripps Research Institute, 1999.
American Association for the Advancement of Science Annual Meeting, 1999.
Bodenstein Lecture, University of Virginia, 1999.
Convocation Address. The University of Chicago, Summer, 1999.
Keynote Address, Rice Institute Symposium, Stress and Human Disease, 1999.
Functional Genomics Symposium, Whitehead Institute, 1999.
Keynote Address, Beckman Institute, University of Illinois, Urbana-Champaign, 1999.
Distinguished Leaders in the Sciences Lecture, National Academy of Sciences, 1999.
Norman Giles Lecturer, The University of Georgia, 1999.
DeWitt Stetten, Jr. Lecture, National Institutes of Health (NIGMS), 1998.
Keynote Speaker: 38th Annual ASCB Meeting, 1998.
Gladstone Distinguished Lecture, University of California - San Francisco, 1998.

SELECTED SERVICE TO THE SCIENCE COMMUNITY

Representative Service on Boards and Committees

Member, MGH Scientific Advisory Committee, 2003–present.
Member, Cold Spring Harbor Laboratory's Board of Trustees, 2002–present.
Member, MIT Computational and Systems Biology Institute Scientific Advisory Board, 2002–present.
Member, Harvard University Radcliffe Institute for Advanced Study Scientific Advisory Board, 2002–present.
Member, Stowers Institute for Medical Research Scientific Advisory Board, 2000–present.
Member, Scientific Advisory Board, Arryx, Inc., 2001–present.
Member, Hereditary Disease Foundation Scientific Advisory Board, 1999–present.
Member, Scientific Advisory Board, Neogenesis, 1998–2001.
Member, American Society of Cell Biology Council, 2001–2002.
Member, Worldbook Encyclopedia ScienceYear Board of Advisors, 2001–2002.
Member, Government-University-Industry Research Roundtable of the National Academy of Sciences, National Academy of Engineering and the Institute of Medicine. 2000–2002.
Member, American Academy of Arts and Sciences, Midwest Council, 1998–2002.
Secretary and Member, Governing Council, Genetics Society of America, 1998–2000.
Member, American Society for Cell Biology, Resource Bureau, 1998–present.
Member and Secretary, Genetics Society of America, 1998-2000.

Commentary, Communication and Public Affairs

Lindquist, S. Strong Unity, Rich Diversity: The Human Genome. September 2000. ***The HHMI Bulletin***. 1: 14 – 15. Reprinted in ***Black Issues in Higher Education.*** December 2000. Vol. 17: 104. Modified from The University of Chicago convocation address, 1999.

Several appearances on radio including *National Public Radio's Science Friday, Here and Now,* and *Odyssey.*

Frequent lectures at universities and high schools worldwide to inform general public, educators, and policy leaders about Biology. Topics included women and a career in science, managing a career and having children, etc. at such institutions as U.C.S.F., Berkeley and MIT. Examples this academic year:

MIT, Independent Activities Period Forums: 1. Advancing the Careers of Women in Science, 2. Balancing Career and Family, Boston, Massachusetts, 2003
Museum of Science, Celebrating DNA 50 Years, Boston, Massachusetts, 2003
AP Biology Faculty Lecture for teachers and students from greater Boston area high schools, 2003
MIT Sloan School Management Conference, Driving Innovation Through Technology, 2003
Brookline High School, lecture to biology students, 2003
Woods Hole, Friday Evening Lectures, 2003
Televised on FCTV 13
Gladstone Institute, lectures to general scientific community and roundtable with students, 2003
Museum of Science, Women in Science Lecture, Boston, Massachusetts, 2002
Whitehead Press Seminar, Evolution: Driving Change, 2002

Consultant and principle in "Lights Breaking", a film on recombinant DNA technology, which received the Gold Medal for best short science film at the San Francisco Film Festival and the Silver Medal for Best Short Science Film at the New York Film Festival, 1985.

Consultant to the Museum of Science and Industry, Chicago, for exhibits on cell biology and genetics, 1983-1987.

Meetings Organized

Chair, Whitehead Institute Annual Symposium: Biological Challenges to Humanity: Emerging and Re-Emerging Pathogens, 2002.

Co-Organizer (with Helen Blau, Rudolf Jaenisch and Harvey Lodish) Catherine A. Stratton Lectures on Critical Issues, sponsored by the MIT Women's League, 2002.

Co-Organizer (with Steven Henikoff) National Academy of Sciences, Arthur M. Sackler Symposium: Self-Perpetuating Structural States in Biology, Disease and Genetics, 2002.

Co-Organizer (with Didier Picard and Johannes Buchner) 1st International Conference on The Hsp90 Chaperone Machine, Arolla, Switzerland, 2002.

Co-Organizer (with Susan Marqusee and Greg Petsko), Protein Society Annual Meeting, Philadelphia, Pennsylvania, 2001.

Co-Chair and organizer (with Paul Fraser), FASEB Symposium on Amyloid Proteins, Copper Mountain, Colorado, 2000.

Co-Chair and organizer (with Art Horwich and Carol Gross), Heat Shock Proteins and Molecular Chaperones, sponsored by Cold Spring Harbor Laboratories, 1998.

Co-Chair and organizer, (with Ralph Isberg) Gordon Conference on Biological Regulatory Mechanisms, Plymouth, New Hampshire, 1996.

Co-Organizer, Heat Shock Proteins and Stress Responses (with Costa Georgopolous and Rick Morimoto), Sponsored by Cold Spring Harbor Laboratories, 1994 and 1996.
Co-Organizer, Rinshoken International Conference on Heat Shock Proteins and Chaperones (with I. Yahara, K. Nagata, and R. Morimoto), Chiba, Japan, 1995.
Co-Organizer, International Symposium on the Function and Regulation of Heat Shock Proteins and Molecular Chaperones (with I. Yahara and K. Nagata), Sponsored by Kyoto University, 1993.
Co-Chair and organizer, Heat Shock Proteins International Symposium (with Bruno Maresca), Sponsored by the Instituti Genetica i Biophysica, Ravello, Italy, 1990.
Program Chair, Annual Meeting of the Genetics Society of America and the Genetics Society of Canada, San Francisco, California, 1990.
Co-Chair and organizer, UCLA Symposium on Heat Shock Proteins, Keystone, Colorado (with M. L. Pardue and J. Feramisco), 1988.
Co-Chair and organizer, Gordon Conference on Biological Regulatory Mechanisms, Plymouth, New Hampshire (with Nigel Grindley), 1985.
Founded and organized the first three meetings of the Midwest Drosophila Conference, Monticello, Illinois, 1982, 1983, and 1984. Meetings have continued on a yearly basis since.
Founded and Co-organized the first two meetings of the Chicago Molecular Biology Symposium, Chicago, Illinois, 1980 and 1981.

Editorial Boards and Professional Societies

Editorial Board: *Public Library of Science*, 2003–present.
Editorial Academy: *Int. Journal of Molecular Medicine*, 1998–present.
Editorial Board: *Molecular Biology of the Cell,* 1996–2001.
Editorial Board: *Current Biology*, 1996–present.
Editorial Board: *Cell Stress and Chaperones*, 1995–present.
Editorial Board: *Gene Expression*, 1994–present.
Editorial Board: *Molecular and Cell Biology*, 1984–present.
Monitoring Editor: *Journal of Cell Biology*, 1993–1998.
Associate Editor: *The New Biologist*, 1991–1993.

American Chemical Society
American Society for Biochemistry and Molecular Biology
American Society for Cell Biology
American Society for Microbiology
American Society of Plant Biologists
American Association for the Advancement of Science
Federation of American Scientists for Experimental Biology
Genetics Society of America
Molecular Medicine Society
Cell Stress and Chaperone Society

Grants and Sponsored Programs

Reviews Granting Agencies: The National Science Foundation, The National Institutes of Health, The Department of Energy, The Department of Agriculture, The March of Dimes Foundation, Human Frontiers in Science Program, The Wellcome Fund, The Keck Foundation.

Argonne National Laboratories, Mechanistic Biology and Biotechnology Review Committee, 1998—2000.

Helen Hay Whitney Postdoctoral Fellowship Review Committee and Scientific Advisory Board, 1997—2002.

Member, Biomedical Sciences Study Section, Subcommittee 3, National Institutes of Health.

Member, Site visit team for the MacArthur Foundation Program for Parasite Biology, 1988-1989.

Member, Special Study Section for Project Center Grants: Stressers, Responders and the Cellular Basis of Disease, National Institutes of Health, 1983.

Member, Genetic Basis of Disease Study Section, National Institutes of Health, 1982.

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